DETAILED ACTION

Response to the Amendment

The Amendment filed on 10/08/2009 in response to the previous Non-Final Office Action (4/28/2009) is acknowledged and has been entered.

Claims 1-10 and 13-22 are pending.

Claims 1-9 and 17-22 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 10 and 13-16 are currently under consideration.

Rejections Withdrawn:

The rejection of claims 10 and 13-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants amendment to remove the term derivative.

The rejection of claims 10 and 13-16 under 35 U.S.C. 103(a) as being unpatentable over Lui et al. (Journal of Labeled Compounds and Radiopharmaceuticals 1998; XLI: 37-45) in view of Getz et al (Analytical Biochemistry 1999; 273: 73-80) and Maurer et al. (WO 02/056907 A2, IDS) as evidenced by Cruse and Lewis (Cruse, Julius and Lewis, Robert. Illustrated Dictionary of Immunology Boca Raton, FL, 1995, of record) has been withdrawn in view of Applicants removal of the term derivative when referring to a chelate.

New Rejections Necessitated by Amendment:

Claims 10 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (US Patent 5,380,513, 1995) in view of Getz et al (Analytical Biochemistry 1999; 273: 73-80) and Maurer et al. (WO 02/056907 A2, IDS) as evidenced by Cruse and Lewis (Cruse, Julius and Lewis, Robert. Illustrated Dictionary of Immunology Boca Raton, FL, 1995, of record).

Gray et al. teach a method of generating a immunoconjugate comprising a radionuclide metal chelate, comprising treating an antibody or fragment with a reducing agent such as DTT or

the like, to produce a free, native sulfhydryl group and reacting said free sulfhydryl group with a maleimido group on the chelating agent (column 8, lines 38-55 and column 10, lines 3-10). For example, the Patent teaches an immunoconjugate having the formula NRML-05(Fab)-N2S2-99mTc, wherein the targeting moiety is a Fab fragment of an antibody, N2S2 is a chelating ligand and 99mTc is a diagnostically active moeity (Example 1, column 10).

Gray et al. does not explicitly teach that the reducing agent is TCEP. Nor does Gray et al. teach the reaction conditions as recited in claims 13-16.

Getz et al. teach a comparison of sulfhydryl reductants tris(2-carboxyethyl)phosphine, e.g., TCEP, and dithiothreitol, e.g, DTT, for use in Protein Chemistry. In particular, Getz et al. teach TCEP offer several advantages over DTT and is the superior reductant when labeling proteins (page 80, 1st column, last paragraph).

Maurer et al. teach a method of coupling Fab fragments to Qβ capsid proteins comprising combining a first solution of a reduced fab fragment generated by reacting a concentration of a Fab fragment, 2.5 mg/mL, at a pH of 7.2 with different concentration (0-1000μM, e.g. 0 mM to 1mM) of either dithiothreitol (DTT) or tricarboxyethylphosphine (TCEP) for 30 minutes at 25°C and a second solution comprising a SMPH derivatized Qβ capsid protein, wherein the final concentration of the protein and Fab were 1.14 mg/mL and 1.78 mg/mL respectively and the reaction proceeded overnight at 25°C (pages 140-141, Example 16). Thus, while Maurer et al. do not explicitly report the Fab concentration in μM or the conjugating moiety concentration in mM, e.g., micromoles/microliter or millimoles/mL, the concentration of the Fab will depend on its molecular weight reported in g/mol which as evidenced by Cruse and Lewis is 47,000 KD, e.g., 47,0000 g/mol (Definition of Fab fragment). Thus, the μM concentration used by the prior art reference is 53μM (See Exhibit I for conversion). In addition, while Maurer et al. do not explicitly report the stoichiometric ratio between the Fab fragment and Qβ capsid protein to be in the range of 1.95 to 2.05, the claimed stiochiometric moar ratio will depend on the molecular weight reported in g/mol which for the reduced Fab fragment is 23,500 Kd and for the protein appears to be about 15,000Kd (see figure 21, marker for Qβ capsid protein. Thus, the stiochiometric ratio used by the prior art is 1 Qβ capsid protein's per 1 Fab fragment (see Exhibit II for conversion).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Gray et al. to include TCEP as the reducing agent instead of DTT in view of the teachings of Getz et al. and Maurer et al. One would have been motivated to do so because in view of the teachings of Getz et al. those of skill in the art recognize that TCEP is the superior reductant for labeling proteins, and further, as taught by Maurer et al., can effectively reduce fab fragments. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Gray et al. to include TCEP as the reducing agent in view of the teachings of Getz et al. and Maurer et al., one would achieve a method for reduction of a fab fragment for direct labeling with ^{99m}Tc.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the reaction conditions for TCEP reduction in view of the teachings of Maurer et al. One would have been motivated to do so because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by optimizing the concentration of the Fab fragment and resultant conjugate moiety, one would achieve the optimal reaction conditions for the conjugation.

Note: In order to expedite prosecution, the Examiner would like to respond Applicants previous arguments as they relate to the present rejection. Regarding Applicants arguments to the references individually, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). With regards to Applicants arguments pertaining to Maurer et al., the Examiner acknowledges Applicants arguments pertaining to stiochiometry of conjugation. However, the Examiner recognizes that Maurer et al.'s stiochiometric ratio of 1.0(e.g., 1 Qβ capsid protein's per 1 Fab fragment, as calculated above) appears to fall with

Applicants claimed range of 0.95 to 1.05. Moreover, the Examiner recognizes that the reaction conditions for the reduction as taught by Maurer et al. appear to fall within the scope of at least claim 13. With regards to Applicants allegations of unexpected results, the Examiner acknowledges Applicants allegations and has reviewed figures 2,4 and 6 of Figure 3 and page 16, lines 8-23 of the specification. However, it is unclear how these results represent unexpected results. In other words, there does not appear to be a comparison between what was expected and Applicants unexpected results. Applicants are directed to MPEP 716.0 2 for providing evidence of unexpected results.

Therefore, No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642